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Association of cardiovascular risk factors and troponin elevation after generalized tonic-clonic seizures

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ABSTRACT

Purpose: Troponins are very sensitive biomarkers of myocardial injury. Conflicting data regarding elevation of troponin levels following a generalized tonic–clonic (GTC) seizure have been reported. In this study we hypothesized that troponin elevation after a GTC seizure occurs more frequently in patients with cardiovascular risk factors.

Methods: Patients who presented to the ER after a single GTC seizure with troponin levels assessed by cardiac troponin T (cTnT) and drawn within 12 h of the GTC seizure were included. Patients with cardiac symptoms, elevated CPK levels or renal insufficiency were excluded. The frequency and risk factors for elevated cTnT levels were analyzed.

Results: Fourteen patients with a mean age of 54 years (range: 19–87 years) were included. Four patients (28.6%) had elevated cTnT levels (mean = 0.06 μg/L; range: 0.035–0.076 μg/L). Patients with elevated cTnT levels were significantly older than those with normal levels (77.5 years vs. 45.5 years; $P = 0.03$). Of the eight patients 60 years of age and older, four (50%) had elevated cTnT levels. The coronary heart disease (CHD) score was significantly higher in patients with elevated cTnT levels compared to those with normal levels (13.5 vs. 9.75, $P = 0.012$).

Conclusions: Elevated troponin levels can occur after a GTC seizure. Patients at risk are the elderly and those with cardiovascular risk factors. Our results suggest that elevation of troponin levels after a GTC seizure reflects a minor ischemic cardiac injury related to the demand ischemia during the sympathetic overactivity that accompanies a GTC seizure.

1. Introduction

Cardiac troponins are specific biochemical markers that are highly sensitive and specific for the diagnosis of acute myocardial infarction.[1–3] However patients with acute neurological illnesses, including rare patients who experienced generalized tonic-clonic (GTC) seizures, were found to have elevations in troponin levels.[4–6] Some have speculated that the troponin elevation following a GTC seizure was secondary to the release of unbound cytosolic troponin due to increased permeability of myocardial cell membranes,[7,8] a centrally mediated damage to myocytes[5] or a false positive assay,[4,8] whereas others have considered this finding as possibly indicative of a transient myocardial injury.[5] Accordingly, the current study was designed to evaluate the significance of elevated troponin as assessed by cardiac troponin T (cTnT) levels following a GTC seizure by comparing the frequency of this finding in young versus elderly patients. Furthermore, we hypothesized that troponin elevation following a GTC seizure would be more frequent in patients with cardiovascular risk factors.

2. Materials and methods

We reviewed all emergency room admissions to the American University of Beirut Medical Center over a period of 6 months and identified patients who presented with a GTC seizure. The diagnosis of a GTC was made based on the description of the spell and clear documentation in the chart of post-ictal confusion. Patients were not included when the description of the spell was unclear, when convulsive syncope was a possibility and when there was no documented evidence of postictal confusion. The medical records of patients who had a cTnT level drawn within 12 h of their seizure (at the discretion of the attending physician staffing the emergency room) were reviewed. Patients with cardiac symptoms, renal insufficiency (creatinine >1.5 mg/dL) or elevated CPK levels

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Table 1
Clinical characteristics of the patients.

Patients	Age (years)	Gender	Hx epilepsy	Cause of sz	Elevated troponin	CHD score
1	19	M	Yes	MTS	No	
2	21	F	Yes	cryptogenic	No	
3	23	F	Yes	Cortical dysplasia	No	
4	25	M	Yes	Cryptogenic	No	
5	28	M	Yes	MTS	No	
6	38	F	Yes	Cortical dysplasia	No	
7	62	M	Yes	Cerebrovascular disease	Yes	11
8	64	F	No	Tumoral	No	8
9	73	M	Yes	Cerebrovascular disease	No	11
10	76	M	No	Cerebrovascular disease	No	10
11	77	F	No	Cerebrovascular disease	Yes	14
12	83	F	No	Alzheimer	No	10
13	84	M	No	Cerebrovascular disease	Yes	14
14	87	M	No	Cerebrovascular disease	Yes	15

Hx: history, sz: seizure, MTS: mesial temporal sclerosis.

(>300 IU/L) were excluded. This study was approved by the Institutional Review Board of the American University of Beirut Medical Center.cTnT was measured on the Elecsys analyzer (Roche, Indianapolis, IN) which allows detection of cTnT concentrations as low as 0.003 μg/L. Based on recent guidelines,[9] cTnT levels of 0.035 μg/L and above were considered abnormal. For patients with cTnT levels of <0.003, a value of 0.003 was assigned for statistical calculations.

We compared the age of patients with normal and elevated cTnT levels via a double tailed t test. We tabulated the cardiovascular risk factors for all patients and calculated the coronary heart disease (CHD) score for patients aged 60 years and older based on a previously described model.[10] This model is a coronary artery disease prediction algorithm, developed using categorical variables including age, cholesterol values, blood pressure, diabetes, and smoking. Based on those categorical variables, a total score stratified by gender can be calculated and was found to be highly predictive for coronary heart disease risk.[10]

Categorical variables for cardiovascular risk factors were compared between patients with normal and elevated cTnT using the exact Fisher's test. The CHD scores for patients 60 years and older with normal or elevated cTnT levels were compared via a two tailed t test. All significant results were set at a P value <0.05.

3. Results

Fourteen patients (M/F = 8/6) with a mean age of 54.3 years (range: 19–87 years) were included in this study (Table 1). Eight of the patients were already diagnosed with epilepsy whereas six presented with their first unprovoked GTC seizure. In patients younger than 60 years, the most common etiologies were mesial temporal sclerosis and cortical dysplasia whereas cerebrovascular disease (remote symptomatic cause) was the cause of seizure/epilepsy in those older than 60 years (Table 1). The mean initial cTnT level, drawn on average 2.8 h (range: 0.7–12 h) after the GTC seizure was 0.021 μg/L (range: 0.003–0.076 μg/L). The mean

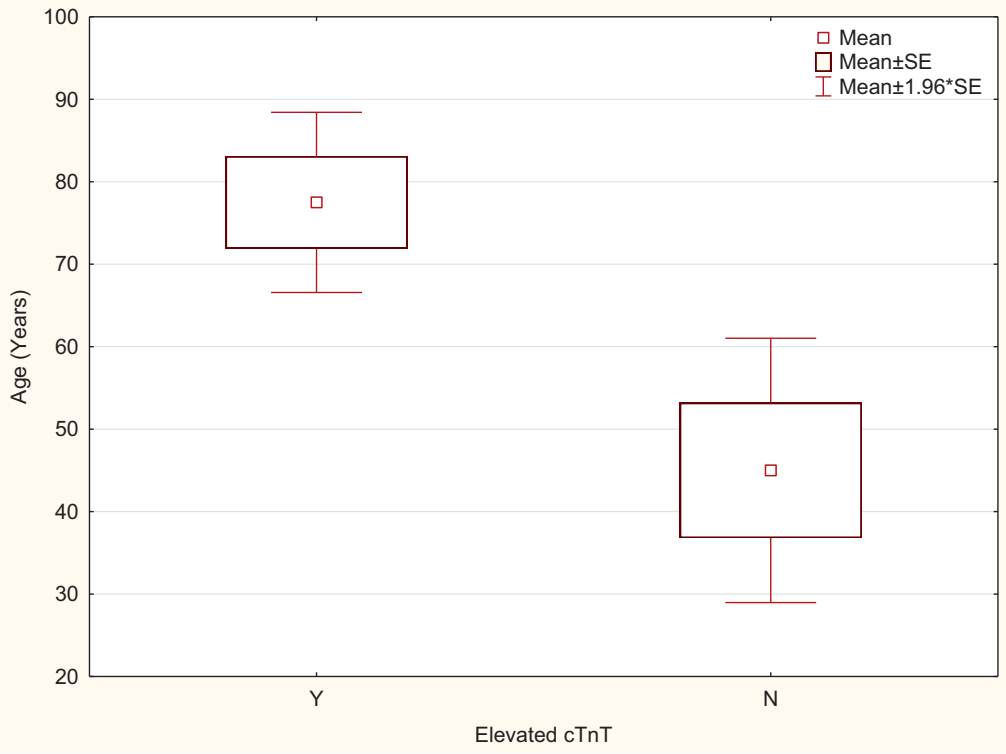

Fig. 1. Box and Whisker plot comparing the mean age (±1.96*standard error) in patients with elevated cTnT to those with normal levels. SE = standard error.

duration of the GTC seizure, as estimated by witnesses, was 1.7 min (range 1–3 min). The ECG on all patients did not reveal any evidence of acute ischemic changes.

The cardiovascular risk factors included diabetes in 3 patients, hypertension in 5 patients, dyslipidemia in 6 patients, smoking in 6 patients, and CAD with previous myocardial infarction in 2 patients. Six patients had no cardiovascular risk factors.

4. Elevated cTnT levels

Four patients (28.6%) had an elevated cTnT level (mean = 0.06 μg/L, range: 0.035–0.076 μg/L). None of those patients had symptoms suggestive of myocardial ischemia. The mean creatinine level for those patients was 0.9 mg/dL (range 0.6–1.5 mg/dL). Patients with elevated cTnT levels remained asymptomatic throughout their hospital stay and echocardiography failed to reveal evidence of regional wall motion abnormalities.

Patients with elevated cTnT levels were significantly older (mean: 77.5 years; range 62–87 years) compared to those with normal levels (mean: 45.5 years; range 19–83 years) ($P = 0.03$) (Fig. 1). There was no significant difference in the time interval from the GTC seizure to blood draw between patients with normal and elevated cTnT levels.

The mean subsequent cTnT levels drawn 40 h (range: 20–58 h) and 66 h (range: 38–95 h) after the GTC seizure dropped to 0.05 μg/L (range: 0.04–0.073 μg/L) and 0.028 μg/L (range: 0.021–0.036 μg/L), respectively.

Hypertension, dyslipidemia and smoking were significantly more frequent in patients with high cTnT levels compared to those with normal levels (Table 2). Although coronary artery disease and a history of previous myocardial infarction were more common in the subgroup of patients with elevated cTnT levels, the difference did not reach statistical significance (Table 2).

Table 2
Frequency of cardiovascular risk factors in patients with elevated cTnT compared to those with normal levels.

Risk factor	Elevated cTnT (4 pts)	Normal cTnT (10 pts)	*P* (Fisher's test)
Diabetes	4	0	$p = 0.001$
HTN	4	1	$p = 0.005$
Dyslipidemia	4	2	$p = 0.015$
Smoking	4	2	$p = 0.015$
CAD	2	0	$p = 0.07$
Previous MI	2	0	$p = 0.07$

5. cTnT levels in elderly

Eight patients (M/F = 5/3) were 60 years and older (mean age: 75 years, range: 62–87 years). Of those, four (50%) had an elevated cTnT level following their GTC seizure. There was no significant difference in the age of patients with elevated cTnT levels (mean: 77 years, range: 62–87 years) compared to those with normal levels (mean age: 74 years, range: 64–83 years).

All four patients with elevated cTnT were diabetics, hypertensive, smokers and had dyslipidemia. In addition two had a history of coronary artery disease and had suffered from a previous myocardial infarction. On the other hand, of the four patients with normal cTnT levels, none was diabetic, one was hypertensive, two had dyslipidemia and one was a smoker. None had a history of coronary artery disease or had suffered from previous myocardial infarction.

The CHD score was significantly higher in patients with high cTnT levels compared to those with normal levels (13.5 vs. 9.75, $P = 0.012$) (Fig. 2).

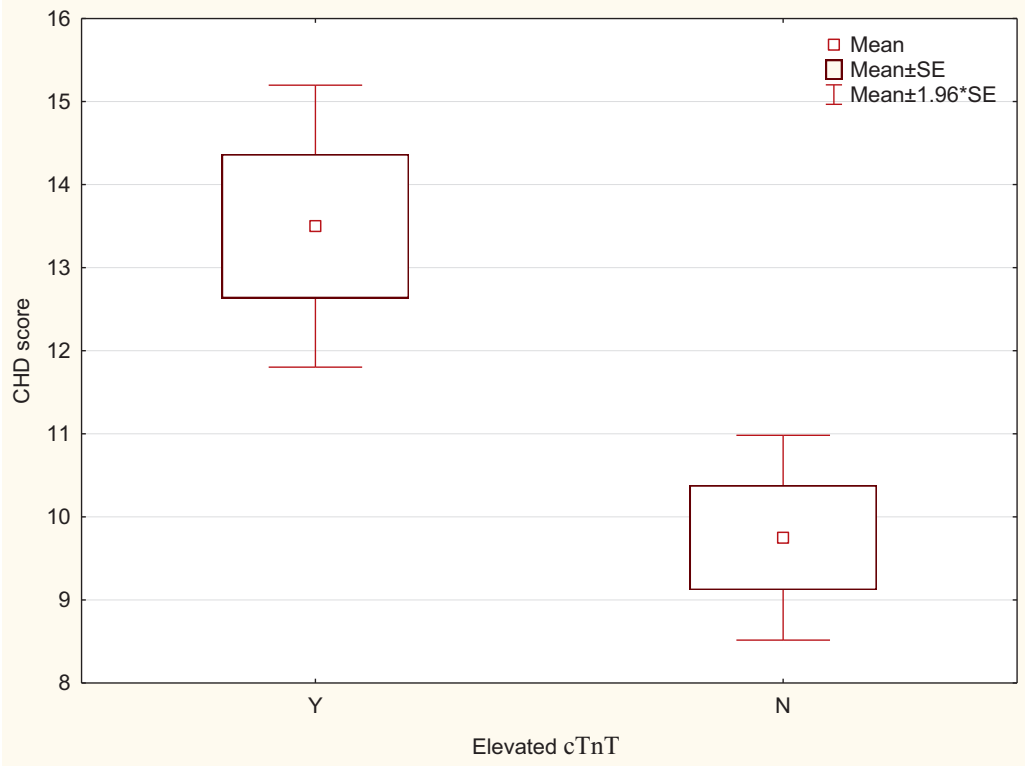

Fig. 2. Box and Whisker plot comparing CHD score (±1.96*standard error) in elderly patients with elevated cTnT to those with normal levels. SE = standard error.

6. Discussion

Our data indicate that cTnT levels are elevated in some patients after a GTC seizure. Those patients were significantly older compared to those with troponin levels within the normal range. In addition, our data show that within the subgroup of elderly patients, those with elevated cTnT levels had significantly higher CHD scores compared to those with normal levels.

Although cardiac troponins are considered the most accurate biomarker of myocardial injury in the clinical setting with a high sensitivity and specificity,[1,2,11] previous studies have documented troponin elevations in conditions other than acute coronary syndromes, including but not limited to rhabdomyolysis[12] pericarditis, myocarditis, sepsis, advanced renal failure, systemic lupus erythematosus, and acute CNS injury such as stroke.[13–16] None of the patients included in this study suffered from those disorders based on strict exclusion criterion and review of the medical records.

A few studies evaluated troponin levels following seizures using sensitive assays. Most of those studies found that the troponin levels remained within the normal range in all patients prompting the conclusion that seizures do not result in troponin levels elevation.[3,6,7,17–19] The common denominator across those studies is that they evaluated young adults[3,7,17] or children and adolescents.[18] For instance, in a study of 11 patients admitted to the epilepsy monitoring unit (4 experienced GTC seizures and 7 complex partial seizures), the mean age of the patients was 34 years with a range between 19 and 55 years.[17] Similarly, in another study that assessed troponin levels following "uncomplicated seizures" (unclear if these were partial or GTC seizures) in 49 patients with normal cardiac system, the mean age of the participants was 21 years with a range from 15–62 years.[3] Likewise, the troponin levels remained in the normal range after a GTC seizure in a cohort of 60 patients with a mean age of 44 years (range not available).[7] Our data in patients younger than 60 years are consistent with those results since none of those had cTnT elevation after a GTC seizure. However, our data indicate that 50% of patients older than 60 years of age have cTnT elevation after a GTC seizure. This age related elevation in cTnT would disfavor the possibility of a "normal physiologic release" of cytosolic release of intracellular unbound cardiac enzymes following a GTC seizure,[7,8] the possibility of a false positive assay[4,8] or the hypothesis of central nervous system mediated transient myocyte injury as described in patients with stroke or cerebral hemorrhage[5] and favor the possibility of a minor ischemic cardiac injury likely related to the perfusion/demand mismatch during the sympathetic over activity that accompanies a GTC seizure. It is logical to assume that elderly patients are more prone to a demand ischemia as compared to younger patients in the setting of a GTC seizure with the associated apnea, tachycardia, and increased blood pressure which will result in increased myocardial oxygen consumption. This hypothesis is further supported by the fact that within the elderly age group, those with higher CHD scores were significantly more likely to have elevated cTnT levels following a GTC seizure.

Our results are very much consistent with those of a recent study that documented elevation of troponin in 6.7% of 741 patients following a GTC seizure.[19] Although patients with elevated CPK levels or renal insufficiency were not excluded from the analyses, there was a significant association between elevation of troponin and baseline CPK levels and vascular risk factors (hypertension, diabetes or dyslipidemia) on logistic regression analysis. None of the patients with elevated troponin had evidence of an acute coronary syndrome despite an extensive work-up that included ECG monitoring, echocardiograms and coronary angiograms in a subset of those patients.[19]

The clinical significance of cTnT elevation following a GTC seizure remains unclear. The absence of cardiac symptoms, normal ECG and echocardiography findings strongly argues against a large transmural myocardial infarction in any of our patients. Few isolated case reports of increased troponin levels following a GTC seizure also failed to document the presence of an acute myocardial infarction in those patients, despite an extensive cardiac work-up including coronary angiography.[4,5] This supports the hypothesis that cardiac biochemical markers are more sensitive than the ECG or echocardiogram in detecting subtle myocardial injury.[15] It is likely that patients with elevated troponin levels following a GTC seizure and no evidence of acute myocardial infarct suffered a type 2 myocardial injury due to demand ischemia secondary to a mismatch between myocardial oxygen demand and supply in the absence of flow limiting coronary artery stenosis.[20] If the patients suffered only from small subendocardial injury or necrosis, it might not be detectable as wall motion abnormality by echocardiography (which requires an infarction thickness of at least 20% of the myocardium) nor by radionuclide imaging which has relatively low resolution for detecting small areas of infarction.[21] Since contrast enhanced cardiovascular MRI was shown to be highly sensitive in detecting subendocardial infarcts missed by single photon emission computed tomography,[22] evaluation of patients with elevated troponin level following a GTC seizure with this modality will help in confirming this hypothesis. Furthermore, a contrast enhanced cardiovascular MRI performed at the time of elevation of troponin levels and repeated a few weeks later will help differentiate between a reversible subendocardial ischemia versus necrosis. If persistent cardiac microlesions are documented, this could favor the onset of cardiac arrhythmias such as ventricular tachyarrhythmias, which in turn could facilitate sudden cardiac death as one cause of sudden unexpected death in epilepsy.[23] Of importance is that patients with elevated troponin levels following an acute neurological illness but without evidence of myocardial infarction were found to have an unfavorable outcome.[6,15,24] Whether this also applies to patients with elevated troponin levels following a GTC seizure will have to be evaluated in prospective longitudinal study.

This study has a number of limitations, in large part due to its retrospective nature. These include its uncontrolled design, the small number of patients included, the absence of a control group (e.g. patients who experienced focal seizures without secondary generalization), the fact that cTnT levels were not uniformly drawn in all patients experiencing a GTC seizure, the time interval variability between the GTC seizure occurrence and the determination of cTnT levels, and the fact that the cTnT were not assessed longitudinally when the initial level was within the normal range. Further prospective longitudinal studies are needed to evaluate the clinical importance of measuring cTnT levels in the context of GTC seizures, especially in the elderly with significant cardiovascular risk factors.

7. Conclusion

GTC seizures appear to induce subtle and subclinical cardiac injury (as assessed by increased cTnT levels) in patients with cardiovascular risk factors. Although clinicians should be aware that an elevation in cardiac enzymes in this setting does not usually indicate the presence of a transmural myocardial infarction, those patients should be carefully investigated by a cardiologist and closely followed up, since reports of acute myocardial infarctions after a GTC seizure have also been reported.[21,25,26]

Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant

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